

FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 13:27:58 ON 14 APR 2006

L1 3356 S (HUMAN TISSUE FACTOR) OR (HUMAN TF) OR (HTF)
L2 523 S L1 (P) ANTIBOD?
L3 13 S L2 (P) (STENOSIS OR RESTENOSIS)
L4 11 S L2 (P) (ANGIOGENESIS OR NEOVASCULARIZATION)
L5 7 DUP REM L3 (6 DUPLICATES REMOVED)
L6 8 DUP REM L4 (3 DUPLICATES REMOVED)

AU Annex B H; Denning S M; Channon K M; Sketch M H Jr; Stack R S; Morrissey J H; Peters K G

SO Circulation, (1995 Feb 1) Vol. 91, No. 3, pp. 619-22.
Journal code: 0147763. ISSN: 0009-7322.

TI Differential expression of tissue factor protein in directional
atherectomy specimens from patients with stable and unstable coronary
syndromes.

AB BACKGROUND: Tissue factor (TF) is a cell membrane-associated protein that catalyzes the rate-limiting step of the extrinsic coagulation pathway, which is the major source of thrombin production in vivo. To explore the potential role that TF may play in ischemic coronary syndromes, directional coronary atherectomy specimens were tested for the presence of TF protein using immunohistochemical techniques. METHODS AND RESULTS: Frozen sections from atherectomy specimens in 61 patients were examined for TF expression using an IgG murine monoclonal antibody against human TF. Patients were classified according to their admission diagnosis as having either an unstable or a stable coronary syndrome. An unstable coronary syndrome was defined as either angina pectoris occurring at rest or post-myocardial infarction (< 1 week) angina. Stable coronary syndromes included patients with stable, progressive, and new-onset (< 6 weeks) angina without rest pain. TF was detected in 15 (43%) of 35 patients with unstable coronary syndromes versus only 3 (12%) of 26 patients with stable coronary syndromes (odds ratio, 5.7; 95% confidence interval, 1.3 to 24.3; P = .018). Within the subgroup of patients with unstable coronary syndromes, TF was detected in 14 (60%) of 25 patients with de novo lesions versus only 1 (10%) of 10 patients with a restenosis lesion (P < .02). An additional 8 patients with stable coronary syndromes due to a restenosis lesion were also negative for TF. Therefore, the overall incidence of TF expression was only 6% (1 of 18) in restenosis lesions compared with 33% (14 of 43) in de novo lesions (P < .03). CONCLUSIONS: This study provides the first description of TF protein expression in human coronary artery lesions in vivo. Tissue factor was readily detected in de novo lesions in patients with unstable coronary syndromes, suggesting a role for TF in the pathogenesis of this disease process. Conversely, TF was rarely detected in patients with restenosis lesions even if the resulting clinical presentation was an unstable coronary syndrome. These results may have implications for the management of patients with unstable angina from de novo lesions and patients with ischemic symptoms from a restenosis lesion.

IN Wong, Hing C.; Jiao, Jin-An; Nieves, Esperanza Liliana; Luepschen, Lawrence

SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2

TI Antibodies for inhibiting blood coagulation and methods of use thereof

AB The invention includes antibodies that provide superior anti-coagulant activity by binding native human TF with high affinity and specificity. Antibodies of the invention can effectively inhibit blood coagulation in vivo. Antibodies of the invention can bind native human TF, either alone or present in a TF: VIIa complex, effectively preventing factor X binding to TF or that complex, and thereby reducing blood coagulation. Preferred antibodies of the invention specifically bind a conformational epitope predominant to native human TF, which epitope provides an unexpectedly strong antibody binding site. The anti-coagulation antibodies are to be used in patients suffering from or susceptible to thrombosis, thromboembolic condition assocd. with cardiovascular disease or infection or neoplasm or use of thrombolytic agent, and restenosis assocd. with invasive medical procedure such as angioplasty, endarterectomy, deployment of a stent, use of catheter, graft implantation or use of an arteriovenous shunt.

- AU Badimon J J; Lettino M; Toschi V; Fuster V; Berrozpe M; Chesebro J H;
Badimon L
- SO Circulation, (1999 Apr 13) Vol. 99, No. 14, pp. 1780-7.
Journal code: 0147763. E-ISSN: 1524-4539.
- TI Local inhibition of tissue factor reduces the thrombogenicity of disrupted human atherosclerotic plaques: effects of tissue factor pathway inhibitor on plaque thrombogenicity under flow conditions.
- AB BACKGROUND: Plaque disruption and subsequent thrombus formation lead to acute coronary syndromes and progression of atherosclerotic disease. Tissue factor (TF) appears to mediate plaque thrombogenicity. Tissue factor pathway inhibitor (TFPI) is the major physiological inhibitor of TF. This study analyzes the role of TF on thrombogenicity of disrupted human atherosclerotic plaques and the therapeutic possibilities of its specific inhibition. METHODS AND RESULTS: Human atherosclerotic and normal arterial segments were exposed to heparinized blood at flow conditions modeling medium-grade coronary stenosis in the Badimon perfusion chamber. The antithrombotic effects of the specific inhibition of plaque TF was assessed by reduction in the deposition of radiolabeled platelets and fibrin(ogen) and immunohistochemical analysis of perfused arteries. TF activity was inhibited by both recombinant TFPI and a polyclonal antibody against human TF. Human lipid-rich plaques were more thrombogenic than less advanced atherosclerotic plaques. Specific inhibition of TF activity reduced plaque thrombogenicity, inhibiting both platelet and fibrin(ogen) deposition (580 versus 194 platelets \times 10⁶/cm²; $P < 0.01$, and 652 versus 172 \times 10¹² molecules of Fg/cm²; $P < 0.05$, respectively) and thrombosis (immunohistochemistry). CONCLUSIONS: This study documents the key role of TF activity in acute arterial thrombosis after atherosclerotic plaque disruption and provides evidence of the benefit of blocking plaque TF activity. Therefore the inhibition of the TF pathway opens a new therapeutic strategy in the prevention of acute coronary thrombosis after plaque disruption.
- IN Jiao, Jian-An; Wong, Hing C.; Nieves, Esperanza Liliana; Mosquera, Luis A.
- SO PCT Int. Appl., 110 pp.
CODEN: PIXXD2
- TI Humanized mouse anti-human tissue factor antibodies and fragments for diagnosis and treatment of blood coagulation-related diseases
- AB The invention includes antibodies that provide superior anti-coagulant activity by binding native human TF with high affinity and specificity. Antibodies of the invention can effectively inhibit blood coagulation in vivo. Antibodies of the invention can bind native human TF, either alone or present in a TF:FVIIa complex, effectively preventing factor X or FIX binding to TF or that complex, and thereby reducing blood coagulation. Preferred antibodies of the invention specifically bind a conformational epitope predominant to native human TF, which epitope provides an unexpectedly strong antibody binding site. Also provided are humanized antibodies and fragments thereof that bind to the TF. The humanized antibodies and fragments are therefore can be used for treating tissue factor-related diseases involving blood coagulation, angiogenesis, tumor metastasis and inflammation.
- AU Almus F E; Rao L V; Pendurthi U R; Quattrochi L; Rapaport S I
- SO Blood, (1991 Mar 15) Vol. 77, No. 6, pp. 1256-62.
Journal code: 7603509. ISSN: 0006-4971.
- TI Mechanism for diminished tissue factor expression by endothelial cells cultured with heparin binding growth factor-1 and heparin.
- AB We have extended our earlier observation that growing primary cultures of human umbilical vein endothelial cells (HUVEC) with heparin binding growth factor 1 (HBGF-1) 20 micrograms/mL and heparin 12 U/mL inhibits expression of tissue factor (TF) activity on HUVEC monolayers perturbed with thrombin. TF activity was measured as the ability of monolayers or cell lysates to support FVIIa-catalyzed activation peptide release from 3H-FX. TF antigen in HUVEC extracts was measured in an enzyme-linked immunosorbent assay (ELISA) that uses a double-antibody sandwich technique with rabbit and goat antibodies to human TF. TF-mRNA was measured by Northern blot hybridization with a 32P-TF cDNA probe. Cells growth with HBGF-1/heparin had both decreased surface and total TF activity as compared with HUVEC from the same endothelial cell pool grown without HBGF-1/heparin. Means \pm SD for TF antigen for four primary cultures were 4.4 \pm 0.9 ng/10⁶ cells without HBGF-1/heparin and 0.6 \pm 0.3 ng/10⁶ cells with HBGF-1/heparin. TF mRNA 4 hours after

incubation with thrombin of HUVEC grown without HBGF-1/heparin was about sevenfold higher than TF mRNA of HUVEC grown with HBGF-1/heparin. These data establish that growing primary cultures of HUVEC with HBGF-1/heparin impairs their ability to synthesize TF apoprotein after perturbation. This may be part of a generalized response of endothelial cells to HBGF-1/heparin facilitating migration during angiogenesis.

- AU Siddiqui, Farooq A.; Francis, John L.
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 258a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
- TI Vascular endothelial growth factor binds tissue factor and enhances its procoagulant activity.
- AB Tissue factor (TF), the membrane-bound glycoprotein that normally initiates the coagulation pathway, is expressed on the surface of various cells including endothelial cells, fibroblasts, monocytes and tumor cells. TF plays an important role in hemostasis, but may also have non-coagulation functions in vascular development, angiogenesis and tumor cell metastasis. Vascular endothelial cell growth factor (VEGF) is a major regulator of angiogenesis. Previous studies have shown that VEGF induced TF mRNA and protein expression in endothelial cells. To explore the relationship between TF and VEGF, we studied the interaction between purified TF and recombinant human VEGF165. Using a dot immunobinding assay, we demonstrated that purified TF-apoprotein from human malignant melanoma cells and recombinant human TF bound to r-human VEGF165. TF-bound VEGF was identified by a specific polyclonal antibody against VEGF165. The binding between TF and VEGF165 was further shown by binding of fluid phase r-human VEGF165 to adsorbed TF-apoprotein (0-2.0 ug/ml) in an enzyme-linked immunoassay (ELISA). The binding was specific, concentration-dependent and saturable. The effect of varying concentrations (0-100 ng/ml) of r-human VEGF165 on the FX-activating activity of purified TF from human malignant melanoma cell was investigated. Recombinant-human VEGF165 enhanced TF-procoagulant activity almost two-fold at a concentration of 50 ng/ml. Specific antibodies against r-human VEGF165 and TF at a concentration of 50 ug/ml inhibited VEGF-TF interaction by 80%. In conclusion, we have shown for the first time that purified r-human VEGF165 selectively binds purified TF-apoprotein and that this enhances the procoagulant activity of TF. The mechanism and physiological significance of this interaction remains to be determined.
- IN Jiao, Jian-An; Wong, Hing C.; Nieves, Esperanza Liliana; Mosquera, Luis A.
SO PCT Int. Appl., 110 pp.
CODEN: PIXXD2
- TI Humanized mouse anti-human tissue factor antibodies and fragments for diagnosis and treatment of blood coagulation-related diseases
- AB The invention includes antibodies that provide superior anti-coagulant activity by binding native human TF with high affinity and specificity. Antibodies of the invention can effectively inhibit blood coagulation in vivo. Antibodies of the invention can bind native human TF, either alone or present in a TF:FVIIa complex, effectively preventing factor X or FIX binding to TF or that complex, and thereby reducing blood coagulation. Preferred antibodies of the invention specifically bind a conformational epitope predominant to native human TF, which epitope provides an unexpectedly strong antibody binding site. Also provided are humanized antibodies and fragments thereof that bind to the TF. The humanized antibodies and fragments are therefore can be used for treating tissue factor-related diseases involving blood coagulation, angiogenesis, tumor metastasis and inflammation.